Chapter 16
Histamine, Serotonin, & the Ergot Alkaloids

自泌素(Autacoid)

- 自泌素(autacoids)由體內自行分泌，藉由組織液以擴散方式運送至附近組織細胞附近，故又稱為局部激素(local hormones)
- 功能
  - 具有生理作用，如局部血液循環的調節、發炎的形成和過敏反應等；當分泌不正常時則產生病理現象

分類

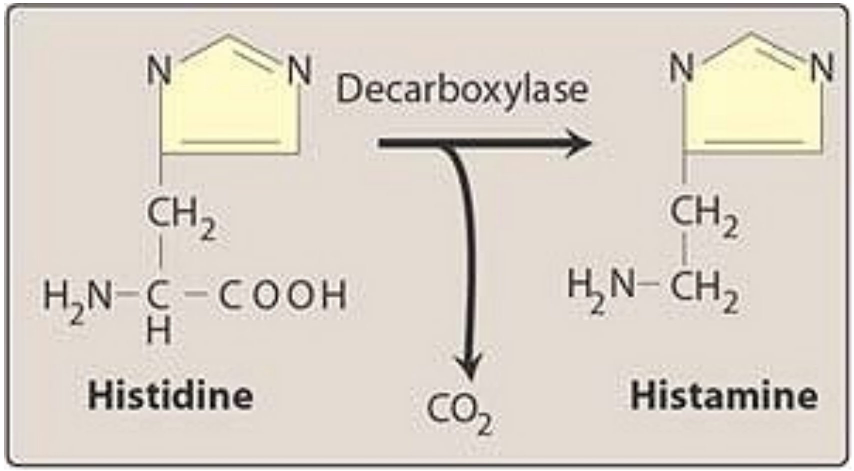
結構	example
胺類	**Histamine**, Serotonin
polypeptide	Angiotensin, endorphin , kinins
不飽和脂肪酸	**Prostaglandin**, Leukotriene, Thromboxane

Histamine

- Early hypotheses
  - i.v.⇨ histamine ⇨ anaphylactic shock and tissue injury
  - possible physiologic roles of tissue histamine
- Histamine is formed from the amino acid histidine is stored
  - in mast cells
  - enterochromaffin cells(腸嗜鉻性細胞) in the gut
  - some neurons,
  - other cell types

- Roles
  - allergic (such as urticaria) and inflammatory reactions
  - gastric acid secretion
  - neurotransmitter and neuromodulator
  - Newer evidence indicates that histamine also plays a role in chemotaxis of white blood cells.

Chemistry & Pharmacokinetics



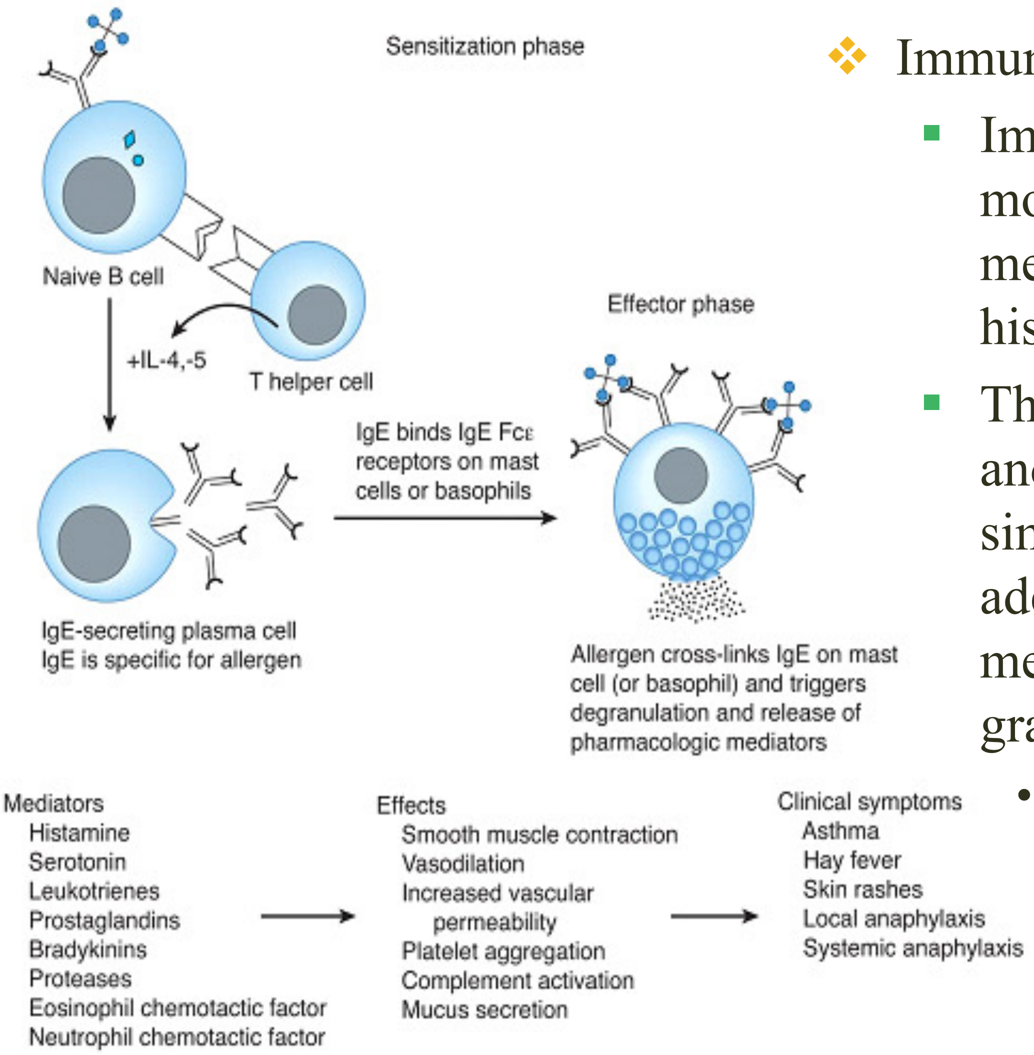
- Histamine occurs
  - in plants
  - in animal tissues

Certain neoplasms (urticaria pigmentosa, myelogenous leukemia…)
→ mast cells or basophils⬆
→ excretion of histamine ⬆.

Mast cells are especially rich at sites of potential tissue injury—nose, mouth, and feet; internal body surfaces; and blood vessels, particularly at pressure points and bifurcations.

- Non-mast cell histamine is found in several tissues, including the brain, where it functions as a neurotransmitter.
  - Strong evidence implicates endogenous neurotransmitter histamine in many brain functions such as neuroendocrine control, cardiovascular regulation, thermal and body weight regulation, and sleep and arousal

Storage & Release of Histamine



- Immunologic Release
  - Immunologic processes account for the most important pathophysiologic mechanism of mast cell and basophil histamine release.
  - This type of release also requires energy and calcium. Degranulation leads to the simultaneous release of histamine, adenosine triphosphate (ATP), and other mediators that are stored together in the granules.
    - Histamine released by this mechanism is a mediator in immediate (type I) allergic reactions, such as hay fever and acute urticaria.

- Chemical and Mechanical Release
  - Certain amines, including drugs such as morphine and tubocurarine, can displace histamine from its bound form within cells.
  - Chemical and mechanical mast cell injury causes degranulation and histamine release. **Compound 48/80,** an experimental drug, selectively releases histamine from tissue mast cells by an exocytotic degranulation process requiring energy and calcium.

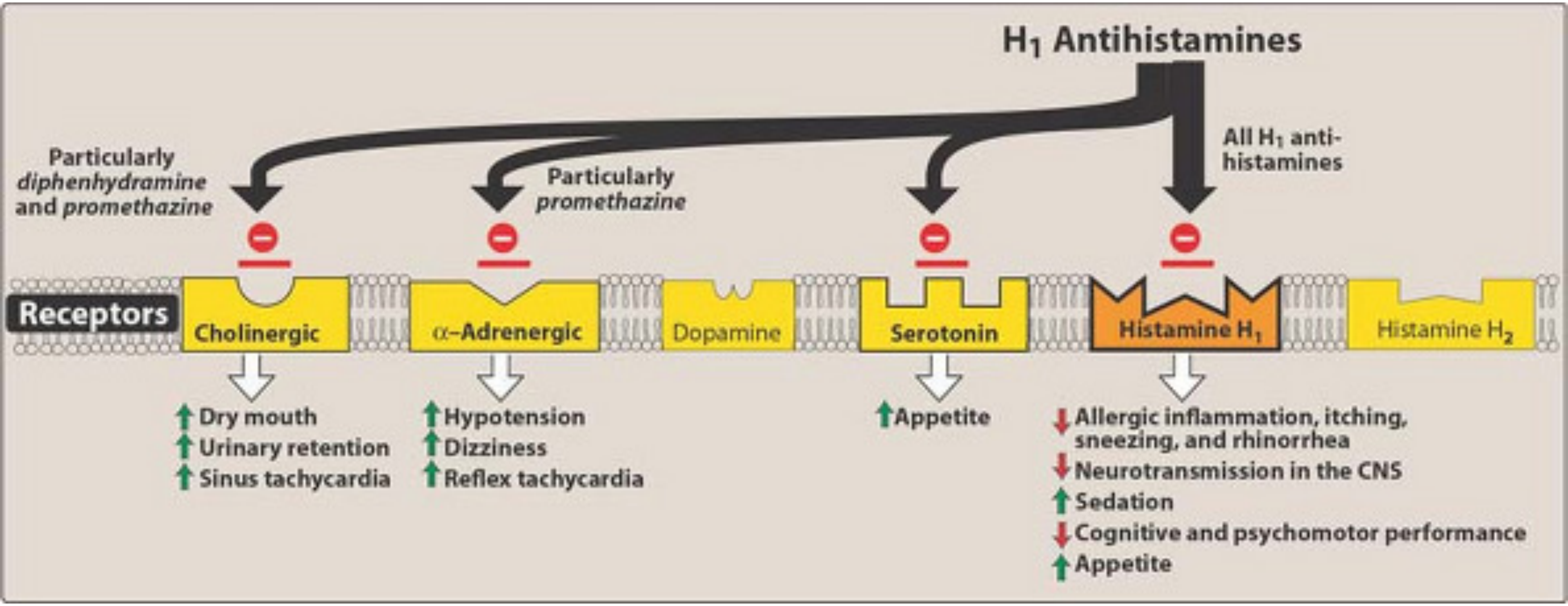
Mechanism of Action

Histamine Receptor Subtypes

Receptor Subtype	Distribution	Postreceptor Mechanisms	Prototypic Antagonist
H_1	Smooth muscle	G_q;↑IP_3, DAG	Diphenhydramine
H_2	Stomach, heart, mast cells	G_s; ↑cAMP	Cimetidine
H_3	Nerve endings, CNS	G_i; ↓ cAMP	Clobenpropit
H_4	Leukocytes	G_i; ↓ cAMP	—

H_1 Receptor

- Allergic reactions
  - This receptor is important in smooth muscle effects, especially those caused by IgE-mediated responses.
  - Typical responses include
    - pain and itching in the skin
    - Bronchoconstriction
    - Vasodilation



H1 Antihistamines
Particularly diphenhydramine and promethazine
Particularly promethazine
All H1 anti-histamines
Receptors
Cholinergic
α–Adrenergic
Dopamine
Serotonin
Histamine H1
Histamine H2
↑ Dry mouth
↑ Urinary retention
↑ Sinus tachycardia
↑ Hypotension
↑ Dizziness
↑ Reflex tachycardia
↑ Appetite
↓ Allergic inflammation, itching, sneezing, and rhinorrhea
↓ Neurotransmission in the CNS
↑ Sedation
↓ Cognitive and psychomotor performance
↑ Appetite

- H_2 Receptor
  - This receptor mediates gastric acid secretion by parietal cells in the stomach
  - has a cardiac stimulant effect
  - A third action is to reduce histamine release from mast cells
    - a negative feedback effect
    - activation of adenylyl cyclase →cAMP ⬆

- H_3 Receptor
  - This receptor appears to be involved mainly in presynaptic modulation of histaminergic neurotransmission in the central nervous system (CNS).
    - Food intake and body weight increase in H_3-receptor knockout animals.
  - In the periphery
    - it appears to be a presynaptic heteroreceptor with modulatory effects on the release of other transmitters
- H_4 Receptor
  - The H_4 receptor is located on leukocytes (especially eosinophils) and mast cells and is involved in chemotactic responses by these cells. Like H3, it is Gi coupled.

Tissue and Organ System Effects of Histamine

1. Nervous System
2. Cardiovascular System
3. Bronchiolar Smooth Muscle
4. Gastrointestinal Tract Smooth Muscle
5. Other Smooth Muscle Organs
6. Secretory Tissue
7. Metabolic Effects

1. Nervous System

- Histamine is a powerful stimulant of sensory nerve endings
  - especially those mediating pain and itching.
- This H_1-mediated effect is an important component of the presynaptic H_3 receptors play important roles in modulating release of several transmitters in the nervous system.
  - H_3 agonists → acetylcholine ⬇ amine ⬇ peptide ⬇ (in various areas of the brain and in peripheral nerves)

2. Cardiovascular System

- In humans→ i.v. histamine → systolic and diastolic blood pressure ⬇, heart rate⬆
  - Mechanism
    - direct vasodilator → blood pressure ⬇ → heart rate ⬆(reflex tachycardia)
- Small doses of histamine → H_1-receptor activation → Vasodilation
- Higher doses of histamine → H_2-receptor activation → direct cardiac stimulation
- In humans
  - the cardiovascular effects of small doses of histamine can usually be antagonized by H_1-receptor antagonists alone.

3. Bronchiolar Smooth Muscle

- In guinea pigs→ histamine → H_1 receptors → bronchoconstriction
- In humans → histamine (small doses)→ normal airways → not marked
    - Such individuals (bronchial hyperreactivity) may be 100 to 1000 times more sensitive to histamine than are normal subjects

4. Gastrointestinal Tract Smooth Muscle

- Histamine →contraction of intestinal smooth muscle
- large doses of histamine → H_1 receptors →diarrhea

5. Secretory Tissue

- Histamine →H_2-receptor → cAMP⬆ → gastric acid secretion

6. The "Triple Response"

- At the site of injection
  - a reddening (dilation of small vessels)
  - edematous wheal (丘疹)
  - red irregular flare surrounding the wheal.
    - The flare is said to be caused by an axon reflex. A sensation of itching may accompany these effects.

Wheal & flare

Clinical Pharmacology of Histamine

- Clinical Uses
  - Histamine has no other current clinical applications.
- Toxicity & Contraindications
- Adverse effects of histamine release, like those following administration of histamine, are dose-related
  - Flushing
  - Hypotension
  - Tachycardia
  - Headache
  - wheals
  - Bronchoconstriction
  - gastrointestinal upset are noted

Histamine receptor

	H_1 receptor	H_2 receptor	H_3 receptor
分布位置	肺、皮膚、肥大細胞	胃黏膜	分佈在突觸前、腦部
生理功能	❖支氣管收縮 ❖微血管通透性增加 ❖與癢、發炎、過敏有關 ❖中樞神經傳遞物質引起嘔吐、暈眩等	❖與胃酸分泌有關 ❖心跳加、快心收縮力增強	❖調節Histamine的釋出 ❖作用尚未明瞭

- 組織胺製劑
  - Betazole用於診斷胃功能
- 抗組織胺製劑
  - Anti-H1
    - First generation
      - Diphenhydramine (Benadryl®)
      - Chlorpheniramine
      - Cyproheptadine (Periactin®)
      - Azatadine
      - Phenindamine (Theophorin®)
      - Cyclizine (Marezine®)
      - Meclizine (Bonamine®)
      - Promethazine
    - Second generation
      - Astemizole (Hismanal®)
      - Terfenadine (Teldane®)
      - Fexofenadine (Allegra®)
      - Loratadine
      - Acrivastine
      - Cetirizine (Zyrtec®)
      - mequitazine

- Anti-H2
  - Cimetidine(Tagamet®)
  - Ranitidine(Zantac®)
  - Famotidine(Gaster®)
  - Nizatidine(Tazac®)

H_1-Receptor Antagonists

- used in the treatment of allergic conditions
  - "cold pills" and sleep aids

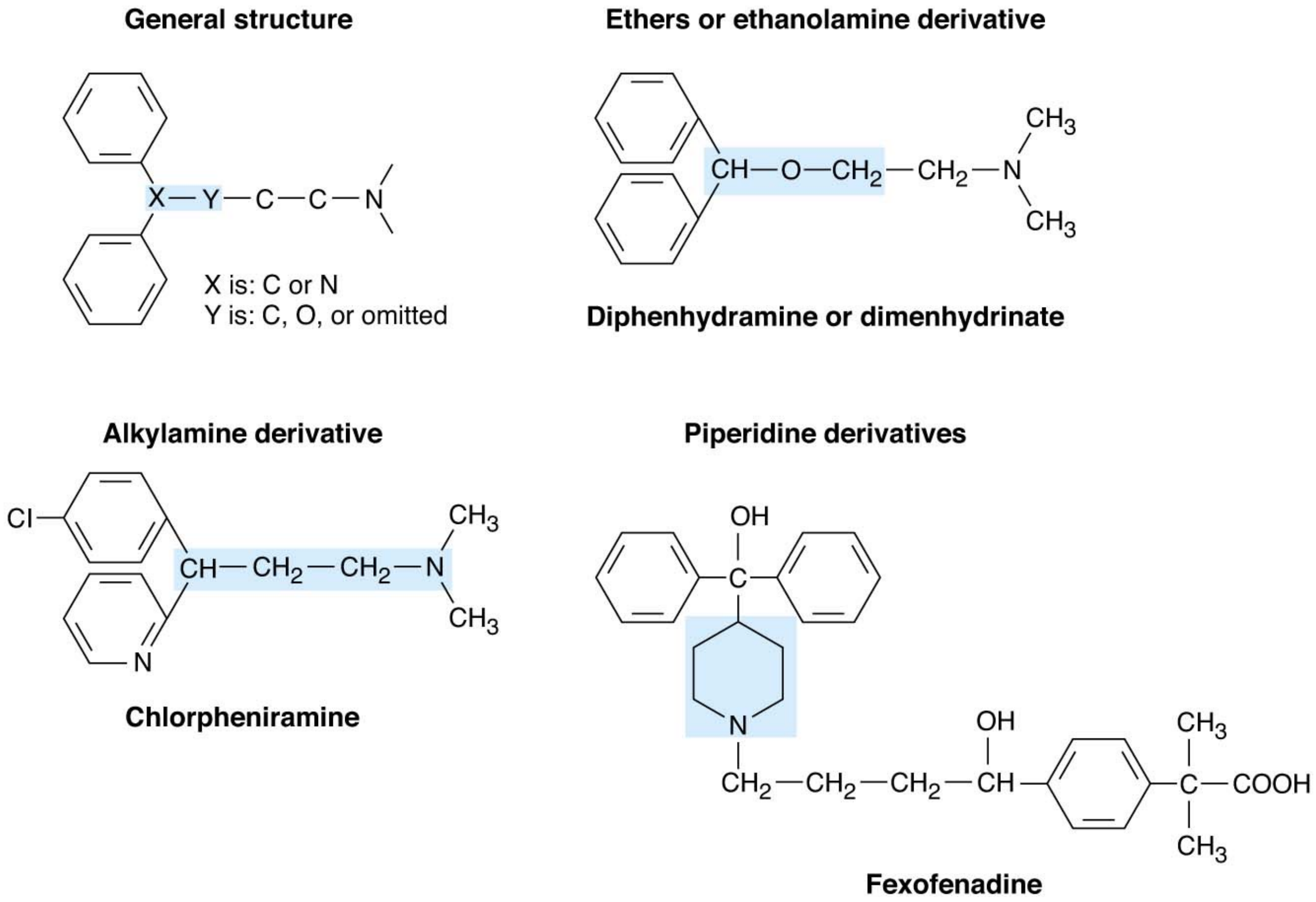
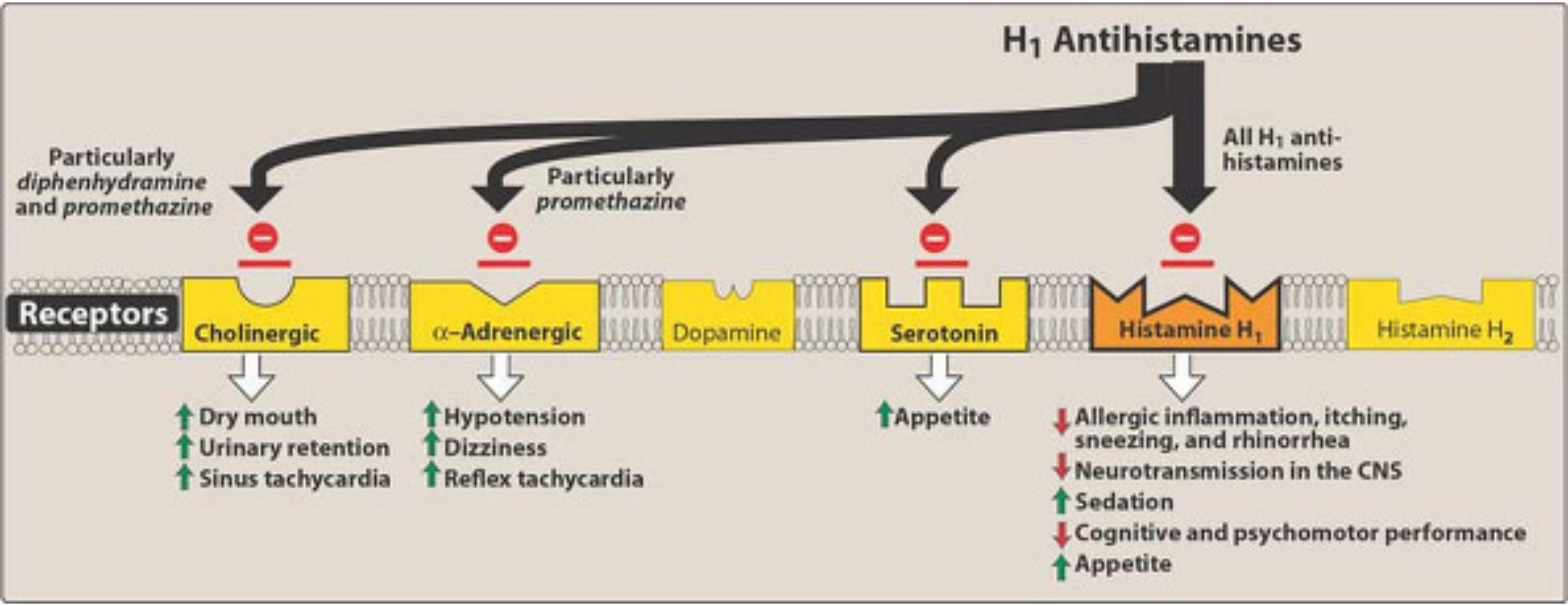


FIGURE 16–1 General structure of H_1-antagonist drugs and examples of the major subgroups. Chemical subgroups are indicated by shading.

Drugs	Dose	Anti-Ach	Comments
FIRST-GENERATION ANTIHISTAMINES			
Carbinoxamine	4–8 mg	+++	Slight to moderate sedation
Diphenhydramine	25–50 mg	+++	Marked sedation; anti-motion sickness activity
Hydroxyzine	15–100 mg	nd	Marked sedation
Cyclizine	25–50 mg	–	Slight sedation; anti-motion sickness activity
Meclizine	25–50 mg	–	Slight sedation; anti-motion sickness activity
Brompheniramine	4–8 mg	+	Slight sedation
Chlorpheniramine	4–8 mg	+	Slight sedation; common component of OTC "cold" medication
Promethazine	10–25 mg	+++	Marked sedation; antiemetic; α block
Cyproheptadine	4 mg	+	Moderate sedation; also has antiserotonin activity

Drugs	Dose	Anti-Ach	Comments
SECOND-GENERATION ANTIHISTAMINES			
Fexofenadine (Allegra)	60 mg	–	
Loratadine (Claritin)	10 mg	–	Longer action
Cetirizine (Zyrtec)	5–10 mg	–	
mequitazine	5 mg		

Pharmacodynamics H_1-Receptor Antagonists



Adrenoceptor-Blocking Actions

Sedation
Antinausea and Antiemetic Actions

Antiparkinsonism Effects

Serotonin-Blocking Action

Local Anesthesia：block sodium channels , potassium channels
OtherActions： inhibit mast cell release of histamine and some other mediators of inflammation

Clinical Pharmacology of H_1-Receptor Antagonists

- Clinical Uses
  - First-generation H1-receptor blocke$_{r}$s are among the most extensively promoted and used over-the-counter drugs.
    - 1th H1-receptor blockers → sedation
    - 2th H1-receptor blockers → weak sedation or nonsedation

1. Allergic Reactions
2. Motion Sickness and Vestibular(前庭) Disturbances
3. Nausea and Vomiting of Pregnancy

First-generation H_1-receptor blockers

- Diphenhydramine
  - 作用
    - 注射治療過敏最佳藥物，強力抑制 CNS，運動困難、另可止吐、止癢。
    - 高血壓及心臟病者須慎用，局部使用易過敏。
    - 與 chlortheophylline 形成之鹽， (dimenhydrinate; Dramamine)，用於暈車及孕婦止吐。
  - 副作用
    - 嗜眠。

- Cyproheptadine
  - 作用
    - 兼具抗 **$5\text{-}HT_2$**，用於止癢。
  - 副作用
    - 鎮靜，停藥後 3～4 天即可消除。
- Azatadine(Zadine)
  - 作用
    - 強效且長效，亦具抗 5-HT，類似 cyproheptadine

- Meclizine
  - 作用
    - 強力抗過敏，起效遲，藥效久（9～24 小時），預防暈車及眩暈。
  - 副作用
    - 嗜眠及阻抑副交感神經。
  - 注意
    - 孕婦、青光眼及無尿患者禁用。
- Cyclizine
  - 作用
    - 預防暈車、暈船及治療術後噁心、嘔吐，而不作抗組織胺用。
  - 副作用
    - 嗜眠及抗膽鹼。

- Promethazine
  - 作用
    - 極強效及長效 phenothiazine 類抗組織胺，廣用於枯草熱、蕁麻疹、暈車船及術後噁心、嘔吐，但不外用局部，以免過敏。
    - 臨睡前服用，藥效維持到第二天全天，然鎮靜嗜眠副作用在第二天清晨即已消退。
    - 有時與 pethidine、chlorpromazine 合併注射，作為麻醉前給藥。對治療帕金森氏病也有效。
  - 副作用
    - 口乾、視覺渾濁，有時嗜眠。
  - 注意
    - 避免與酒併服。

Second-generation H1-receptor blockers

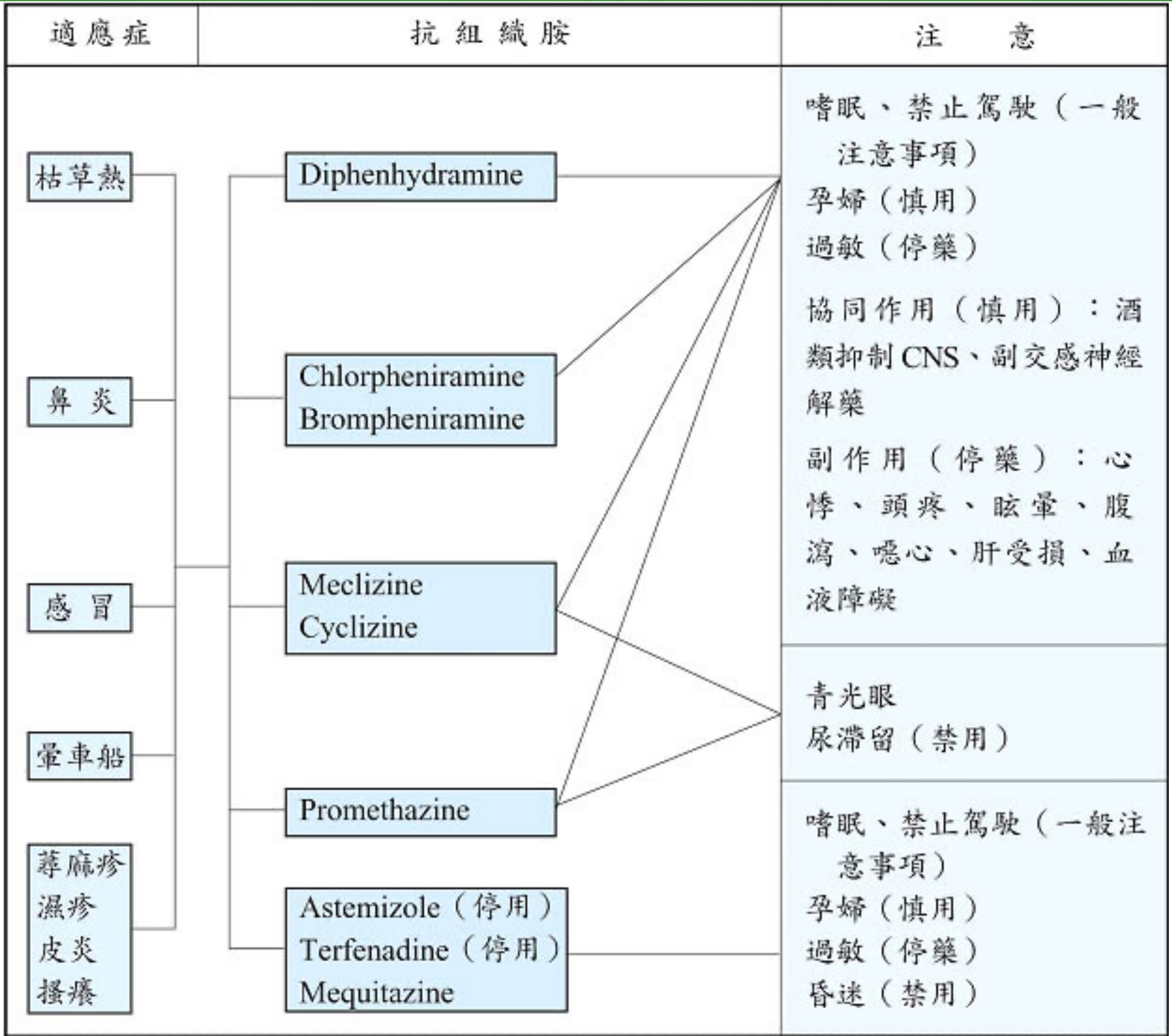
- Fexofenadine (Allegra®)
  - 作用
    - 為 terfenadine 活性代謝物，作用亦類似，但本藥不經代謝即有藥效，因之無心毒性。
    - 吸收不受食物影響，多以原態經糞便及尿排泄，適於肝功能不全病人，但腎功能不良者需減量。
  - 副作用
    - 噁心、疲倦、消化不良、病毒感染、經痛。

- Loratadine
  - 作用
    - 由第一代藥 azatadine 及 cyproheptadine 修飾結構而得，已無 CNS 副作用。
    - 藥效極佳，另有抗 5-HT 作用。

- Acrivastine
  - 作用
    - 結構、藥效、作用時限均類似 triprolidine，但抗 ACh 及嗜眠副作用低。
    - 與去鼻充血劑 pseudoephedrine 口服併用。

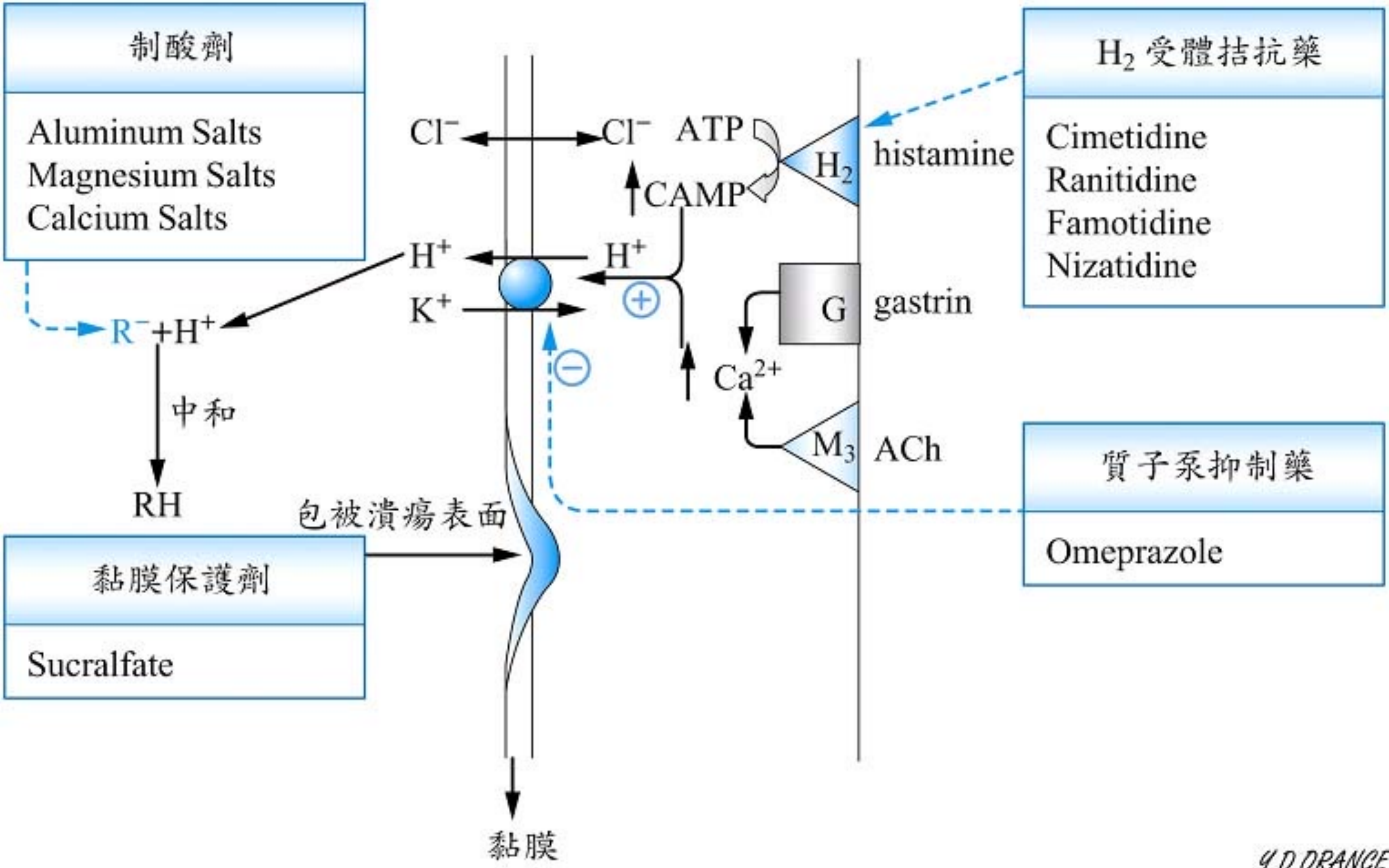
- Cetirizine (Zyrtec®)
  - 作用
    - 為第一代藥 hydroxyzine 代謝物，但不穿透 BBB。
    - 優點為作用快速，每日只需服用一次，無心毒性、無 CNS 毒性。
  - 副作用
    - 嗜眠、倦怠、口乾、眩暈。
  - 注意
    - 駕駛或機械操作者需慎用
- Mequitazine (Primalan)
  - 作用
    - 屬於 phenothiazine 類，不通過 BBB，不引起鎮靜，藥效很長（24 小時）。
    - 口服 6 小時後達最高血中濃度，輕微抑制副交感神經。在 10 mg 劑量時產生輕微鎮靜嗜眠，因此治療範圍狹窄

Anti-histamine



H_2-Receptor Antagonists

- The development of H_2-receptor antagonists
  - was based on the observation that H_1 antagonists had no effect on histamine-induced acid secretion in the stomach.
  - Cimetidine, Ranitidine and other H2 antagonists
    - must be used cautiously in patients with hepatic impairment and adjust dosage in patient with renal impairment.
  - Inhibition of hepatic metabolism of warfarin, diazepam, propranolol, theophylline, and other drugs metabolized by hepatic mixed-function oxidase system



制酸劑
Aluminum Salts
Magnesium Salts
Calcium Salts
Cl^-
Cl^-
ATP
CAMP
H^+
H^+
K^+
$R^- + H^+$
中和
RH
包被潰瘍表面
黏膜保護劑
Sucralfate
黏膜
H_2
histamine
G
gastrin
Ca^{2+}
M_3
ACh
H_2 受體拮抗藥
Cimetidine
Ranitidine
Famotidine
Nizatidine
質子泵抑制藥
Omeprazole

Y.D.DRANCE

H2受體拮抗劑

- Cimetidine (Tagamet®), Ranitidine (Zantac®)
  - 作用
    - 藥效相當，口服或注射，以 Ranitidine 之副作用較少，療效極佳 (70～90%)，藥效長達七小時，為治療首選藥
    - Ranitidine 較 cimetidine 長效，服藥次數較少，不抑制肝代謝的酵素，因而沒有藥物相互作用。本藥無抗雄性激素效應，不造成男性女乳或陽痿
    - Cimetidine 抑制肝 cytochrome P450 氧化酵素系統，造成嚴重的藥物相互作用（表 9-3）
    - Cimetidine 的適應症包括：
      - 短期治療十二指腸潰瘍
      - 預防十二指腸潰瘍復發
      - 治療過度分泌，例如 Zöllinger-Ellison 症候群
  - 副作用
    - Cimetidine 短期用藥幾無副作用；長期（一年）可致男子女乳症 (gynecomastia)、陽痿，停藥後可恢復正常

- Famotidine (Gaster®)
  - 作用
    - 口服或 IV 效果極佳，藥效更強久，並增進胃粘膜的防禦力，劑量僅需每天二次，每次 20 mg。副作用更少，是最佳 H2 拮抗劑
- Nizatidine (Tazac®)
  - 作用
    - 口服生體可用率極佳 (>90%)，無抗雄性激素效應或抑制 cytochrome P450 氧化酵素

項　　目	Cimetidine	Ranitidine	Famotidine
初劑量	400 mg × 2 或 200 mg × 3 + 400 mg	150 mg × 2	20 mg × 2
最大劑量	400 mg × 3	300 mg × 3	
維持量	睡前 400 mg	睡前 150 mg	
相對抑酸活性	1	12	72.6
口服半生期（小時）	2.2	2～2.5	3.3
十二指腸潰瘍治癒率 (%)	45～84（四週） 92～95（八週）	63～78（四週） 85～92（八週）	
高血泌乳素	+	−	−
抗雄性素效應	+	−	−
抑制藥物肝代謝	+	−	−
副作用發生率 (%)	3.7	3.8	2.5

Clinically important Drug interactions with Cimetidine

Drug	Mechanism	Clinical significance
Tricyclic Antidepressants	Clearence ↓	↑ Side effect
Benzodiazepines	Clearence ↓	↑ sedation
Phenytoin	Clearence ↓	↑ Toxicity
Ketoconazole	Absorption ↓	↓ Effect
Metronidazole	Clearence ↓	Unknown
Lidocaine	Clearence ↓	↑ Toxicity
Quinidine	Clearence ↓ (Hepatic & renal)	Prolonged QT interval
Labetalol	Unclear	↓ Blood pressure
Propranolol	Clearence ↓	hypotension, bradycardia
Nifedipine	↑ AUC 60%	↑ Effect
Verapamil	Clearence ↓ 21% ↓ metabolism	No dynamic effects reported
Theophylline	Clearence ↓	↑ Toxicity
Warfarin	Clearence ↓	↑ Prothrombin time

治療

- 必須使用抗生素來去除幽門螺旋菌
  - amoxicillin、 tetracycline、metronidazole …
- 二合一療法
  - 一種抗生素加上一種輔助藥物 (Tagamet 、 Zantac 、 Losec…)
- 三合一療法
  - 二種抗生素加上一種輔助藥物
- 四合一療法
  - 二種抗生素加上二種輔助藥物

2週療程

Used for H. pylori & Ulcers

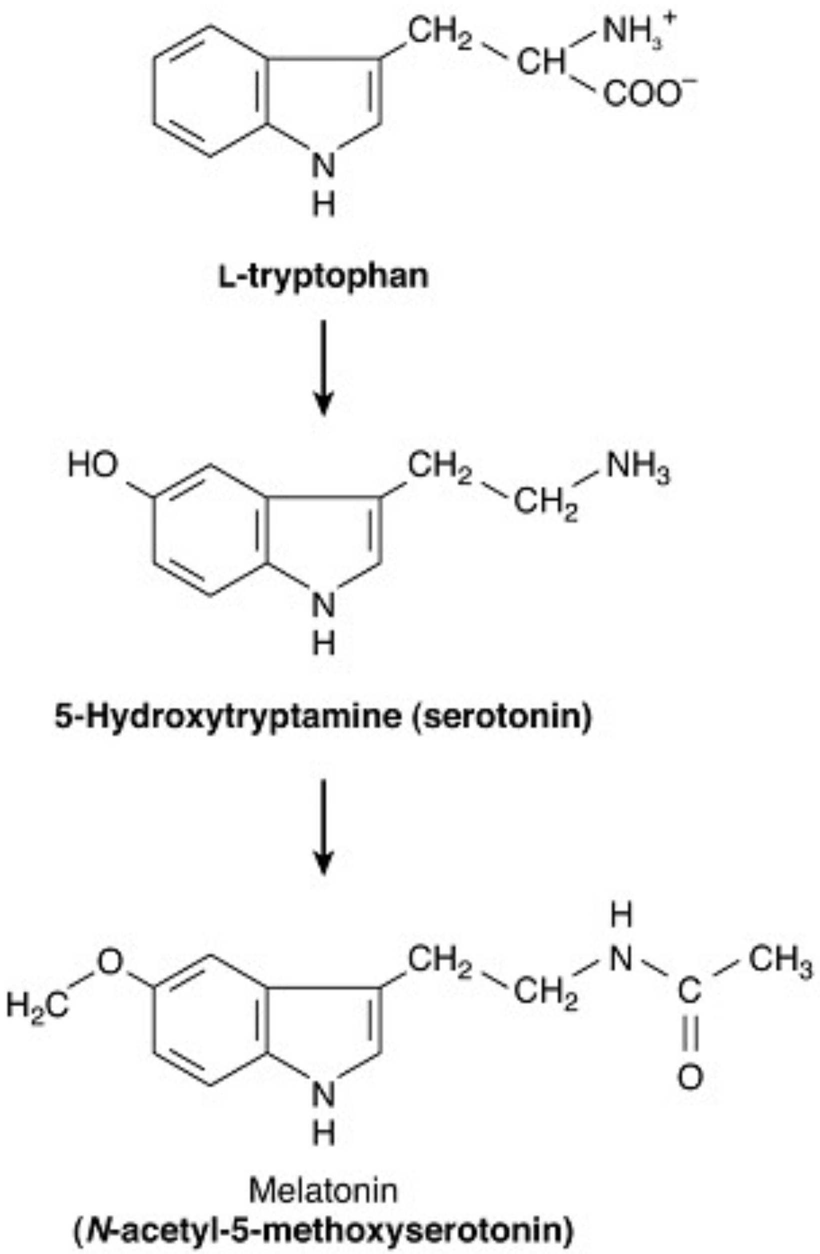
Drug 1	Drug 2	Drug 3	Drug 4	Duration	Efficacy
Bismuth 2 tab. QID	Metronidazole 250 mg TID/QID	Tetracycline * 500mg QID	Omeprazole 20 mg BID	1-2 weeks	94-98%
Bismuth 2 tab. QID	Metronidazole 250 mg TID/QID	Amoxicillin 500mg TID/QID		1 week 2 weeks	75-81% 80-94%
Bismuth 2 tab. QID	Clarithromycin 500mg TID	Tetracycline * 500mg QID		1-2 weeks	> 90%
Bismuth 2 tab. QID	Clarithromycin 500mg TID	Amoxicillin 500mg QID		1-2 weeks	> 90%
Bismuth 2 tab. QID	Clarithromycin 500mg BID	Omeprazole 20 mg BID		8 days	80 %
Metronidazole 500 mg BID	Omeprazole 20 mg BID	Clarithromycin 250mg BID		1-2 weeks	85-91 %
Amoxicillin 1 gm BID	Omeprazole 20 mg BID	Clarithromycin 500mg BID		1-2 weeks	80-95 %
Amoxicillin 1 gm BID	Omeprazole 20 mg BID	Metronidazole 500 mg BID		1-2 weeks	77-86 %
Amoxicillin 500mg TID	Omeprazole 40 mg daily			2 weeks	54-79 %
Amoxicillin 500mg QID	Clarithromycin 500mg TID			2 weeks	> 90 %
Amoxicillin 700mg TID	Metronidazole 500 mg TID			2 weeks	> 85%
Clarithromycin 500mg TID	Omeprazole 40 mg daily			2 weeks	83%
Clarithromycin 500mg TID	Ranitidine 150 mg BID			2 weeks	82-94%

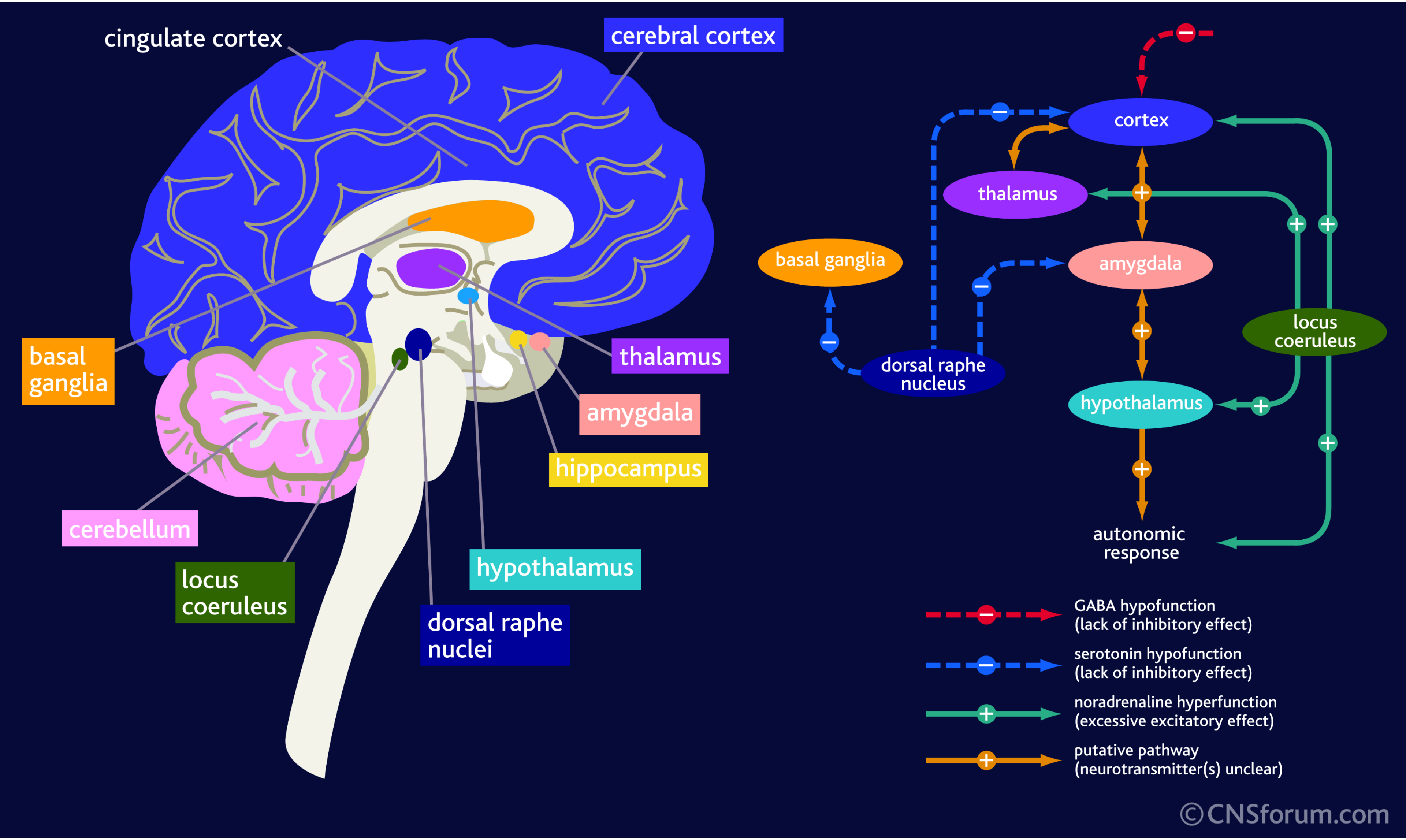
H_3 & H_4-Receptor Antagonists

- Although no selective H_3 or H_4 ligands are presently available for general clinical use, there is great interest in their therapeutic potential.
  - H_3-selective ligands may be of value in sleep disorders, obesity, and cognitive and psychiatric disorders.
    - Tiprolisant, an inverse H_3-receptor agonist, has been shown to reduce sleep cycles in mutant mice and in humans with narcolepsy.
    - Increased obesity has been demonstrated in both H_1- and H_3-receptor knockout mice.
  - H_4 blockers have potential in chronic inflammatory conditions such as asthma, in which eosinophils and mast cells play a prominent role.
    - Several studies have suggested that H_4-receptor antagonists may be useful in pruritus (搔癢).

Serotonin (5-Hydroxytryptamine)

- Serotonin is an important neurotransmitter, a local hormone in the gut, a component of the platelet clotting process, and is thought to play a role in migraine headache
  - over 90% of the serotonin in the body is found in enterochromaffin cells in the gastrointestinal tract
  - serotonin is also found in platelets ,in the raphe nuclei of the brain stem
  - A few foods contain




cingulate cortex
cerebral cortex
basal ganglia
thalamus
amygdala
hippocampus
cerebellum
hypothalamus
locus coeruleus
dorsal raphe nuclei
cortex
thalamus
basal ganglia
amygdala
locus coeruleus
dorsal raphe nucleus
hypothalamus
autonomic response
GABA hypofunction (lack of inhibitory effect)
serotonin hypofunction (lack of inhibitory effect)
noradrenaline hyperfunction (excessive excitatory effect)
putative pathway (neurotransmitter(s) unclear)
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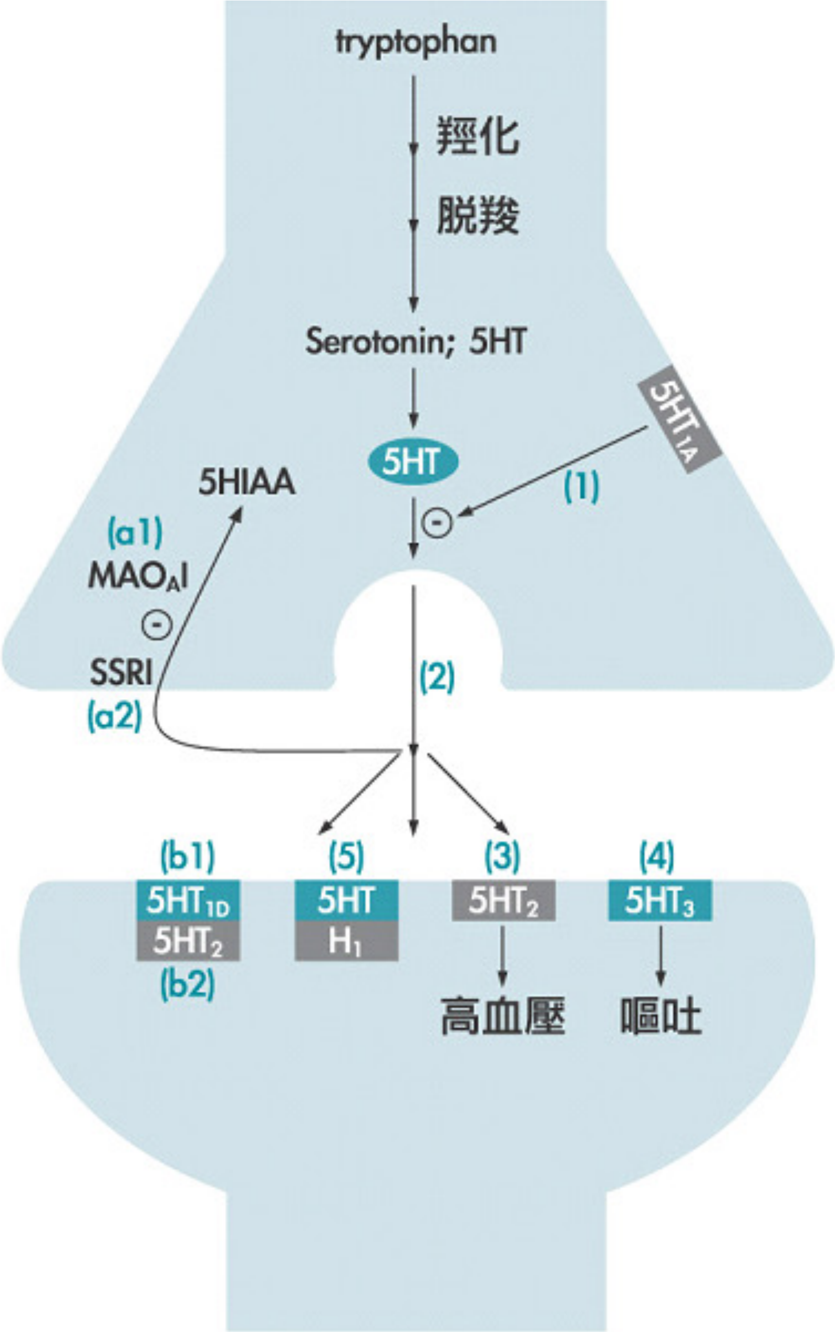
Mechanisms of Action

Receptor Subtype	Distribution Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-HT_{1A}	Raphe nuclei, hippocampus; G_i, cAMP	8-OH-DPAT	WAY100635
5-HT_{1B}		Sumatriptan, CP93129	
5-HT_{1D}	Brain; G_i, cAMP	Sumatriptan	
5-HT_{1E}			
5-HT_{1F}		LY334370	
5-HT_{1P}	Enteric nervous system; G_o, slow EPSP	5-Hydroxyindalpine	Renzapride
5-HT_{2A}	Platelets, smooth muscle, cerebral cortex; G_q, IP_3	α-Methyl-5-HT	Ketanserin
5-HT_{2B}	Stomach fundus; G_q, IP_3	α -Methyl-5-HT	SB204741
5-HT_{2C}	Choroid, hippocampus, substantia nigra; G_q, IP_3	α -Methyl-5-HT	Mesulergine
5-HT_3	Area postrema, sensory and enteric nerves Receptor is a Na^+-K^+ ion channel	2-Methyl-5-HT, m-chlorophenylbiguanide	Granisetron, ondansetron, tropisetron
5-HT_4	CNS and myenteric neurons, smooth muscle; G_s, cAMP	5-Methoxytryptamine, renzapride, metoclopramide	
5-$HT_{5A,B}$	Brain, cAMP		
5-$HT_{6,7}$	Brain, G_s, cAMP		Clozapine (5-HT_7)



增加5HT在突觸間隙及受體致效劑

A. 抗憂鬱藥

(a1) 減少被分解MAO_AI，Moclobemide

(a2) 抑制再回收SSRI，Fluoxetine

B. 預防及治療偏頭痛

(b1) $5HT_{1D}$受體致效劑，Sumatriptan

(b2) $5HT_2$部份致效劑，Methysergide

降低5HT在突觸間隙間及拮抗劑

(1) $5HT_{1A}$部份致效劑(迴饋抑制5HT釋出)，Buspirone(抗焦慮)

(2) 排空5HT致被分解，Resepine(降血壓)

(3) $5HT_2$受體拮抗劑，Ketanserin. Ritanserin(降血壓)

(4) $5HT_3$受體拮抗劑，Ondansetron(止吐)

(5) 5HT及H_1拮抗劑，Cyproheptadine(抗過敏)

Tissue and Organ System Effects Serotonin

- Nervous System
  - $5\text{-}HT_3$ receptors in the gastrointestinal tract and in the vomiting center of the medulla participate in the vomiting reflex (**chemoreceptor reflex**).
    - They are particularly important in vomiting caused by chemical triggers such as cancer chemotherapy drugs.
      - 5-HT3 antagonist
        - Ondansetron (zofran®)
  - $5\text{-}HT_{1P}$ and $5\text{-}HT_4$ receptors also play important roles in enteric nervous system function
  - **Melatonin**
    - Activation of the MT_1 receptor results in sleepiness, whereas the MT_2 receptor may be related to the light-dark synchronization of the biologic circadian clock
    - **Ramelteon** is a selective MT_1 and MT_2 agonist that is approved for the medical treatment of insomnia.

- 副作用
  - 頭痛、感覺燥熱與潮紅、便秘；若是注射劑，靜脈注射部位出現局部反應
- 注意事項
  - 對於中度或重度肝功能損害者，對於這類患者每日劑量不可超過8mg。

- Cardiovascular System
  - Serotonin→5-HT_2 receptors→contraction of vascular smooth muscle
    - 5-HT_2 antagonist
      - Ketanserin (Sufrexal®)
  - A triphasic blood pressure response (injection of serotonin)
    - heart rate, cardiac output, and blood pressure ⬇
    - pressure increases (vasoconstriction) ⬆
    - blood pressure ⬇ (vasodilation in vessels supplying skeletal muscle)
  - Serotonin causes blood platelets to aggregate by activating **5-HT_2** receptors

- Respiratory System
  - Serotonin has a small direct stimulant effect on bronchiolar smooth muscle in normal humans, probably via 5-HT_{2A} receptors
- Gastrointestinal Tract
  - Serotonin is a powerful stimulant of gastrointestinal smooth muscle, increasing tone and facilitating peristalsis.
    - Serotonin→5-HT_2 smooth muscle receptors, enteric nervous system
- Skeletal Muscle
  - 5-HT_2 receptors are present on skeletal muscle membranes, but their physiologic role is not understood.
  - **Serotonin syndrome** (MAO inhibitors, SSRIs…..)

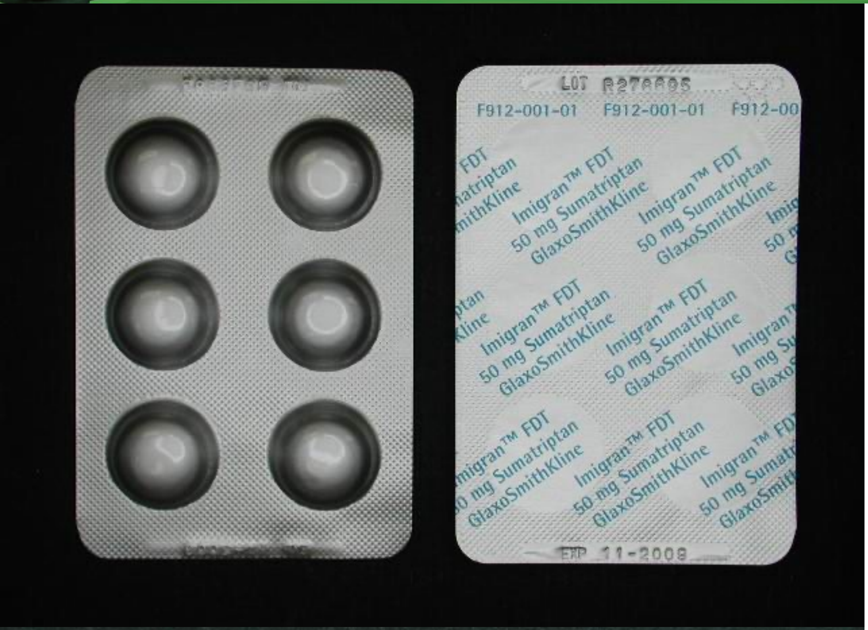
    →skeletal muscle contractions
      - Although the hyperthermia of serotonin syndrome results from excessive muscle contraction, serotonin syndrome is probably caused by a central nervous system effect of these drugs

Characteristics of Serotonin Syndrome and Other Hyperthermic Syndromes

Syndrome	Precipitating Drugs	Clinical Presentation	Therapy
Serotonin syndrome	SSRIs, second generation antidepressants, MAOIs, linezolid, tramadol, meperidine, fentanyl, ondansetron, sumatriptan, MDMA, LSD, St. John's wort, ginseng	Hypertension, hyperreflexia, tremor, clonus, hyperthermia, hyperactive bowel sounds, diarrhea, mydriasis, agitation, coma; onset within hours	**Sedation (benzodiazepines), paralysis, intubation and ventilation; consider 5-HT**$_2$ block with cyproheptadine or chlorpromazine
Neuroleptic malignant syndrome	D_2-blocking antipsychotics	Acute severe parkinsonism; hypertension, hyperthermia, normal or reduced bowel sounds, onset over 1–3 days	**Diphenhydramine (parenteral), cooling if temperature is very high, sedation with benzodiazepines**
Malignant hyperthermia	Volatile anesthetics, succinylcholine	Hyperthermia, muscle rigidity, hypertension, tachycardia; onset within minutes	**Dantrolene, cooling**

Clinical Pharmacology of Serotonin

- **Buspirone**
  - Mechanism
    - 5-HT_{1A} agonist
  - Clinical Applications
    - Anxiolytics
- **Sumatriptan (triptans), <u>ergot alkaloids</u>**
  - Mechanism (5-$HT_{1D/1B}$ agonist)
    - may activate 5-HT_{1D}/$_{1B}$ receptors on presynaptic trigeminal nerve endings to inhibit the release of vasodilating peptides
    - the vasoconstrictor actions of direct 5-HT agonists (the triptans and ergot) may prevent vasodilation and stretching of the pain endings
  - Clinical Applications
    - in the treatment of acute migraine and cluster headache attacks



<u>建議劑量</u>

成人：單次最多服用100 mg；若二小時後症狀未緩解，可再服用第二劑，但每日不可超過300 mg。建議sumatriptan每週不可服用超過兩天。

兒童：Sumatriptan對16歲以下兒童的安全性及有效性尚未確立。

健保限制需符合下列規定，才可依健保給付sumatriptan之治療：

一、 限成人符合國際頭痛協會(InternationalHeadache Society)1988年訂定的「偏頭痛」診斷標準者：

A.至少有五次能符合B至D項的發作。

B.頭痛發作持續四至七十二小時。

C.頭痛至少具下列二項特徵：

1. 單側
2. 搏動性
3. 程度中等或重度(日常生活受限制甚或禁絕)
4. 上下樓梯或類似之日常活動會使頭痛加劇

D.當頭痛發作時至少有下列情形之一：

1. 噁心或嘔吐
2. 畏光及怕吵

二、偏頭痛之發作嚴重影響日常生活(無法工作或作家事)者。

三、經使用其他藥物無效者。

四、每月限使用一次，每次處方不超過100mg。

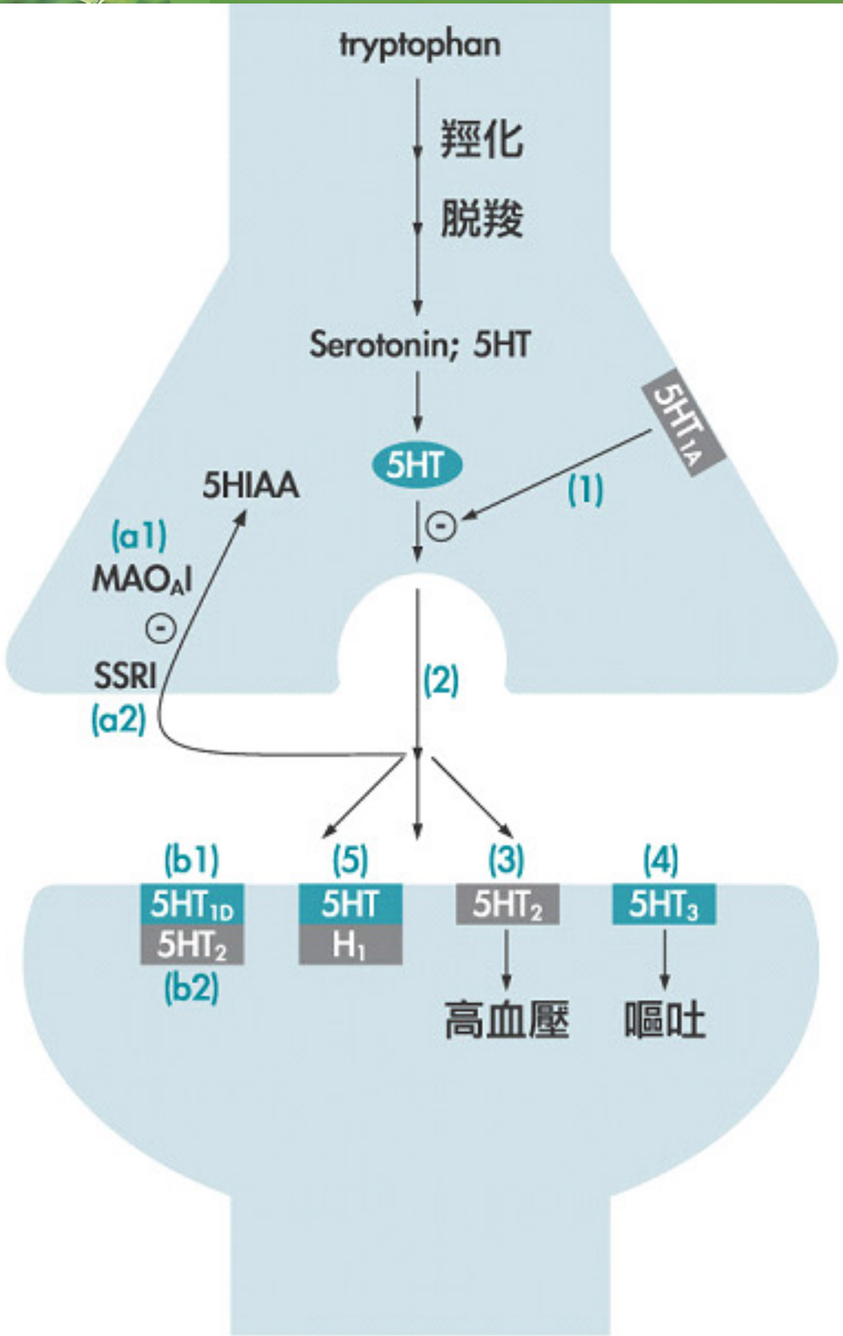
五、不得同時處方含有ergotamine 或其衍生物之製劑。

六、不得作為預防性使用。

七、不得使用於曾患有心肌梗塞、缺血性心臟病、Prinzmetal氏狹心症、冠狀血管痙攣者及高血壓未受控制的患者。

Cisapride

- Mechanism
  - a 5-HT_4 agonist
- Clinical Applications
  - was used in the treatment of gastroesophageal reflux (胃食道逆流) and motility disorders
- Toxicity
  - Arrhythmia
- Drugs
  - **Mosapride**
  - **Tegaserod**
    - irritable bowel syndrome with constipation (激躁性結腸症)



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Serotonin-Receptor Antagonists

- **Cyproheptadine**
  - Mechanism
    - H_1-receptor-blocking as well as 5-HT_2-blocking action
- **Ketanserin**
  - Mechanism
    - blocks 5-HT_2 receptors
    - blocks α_1 adrenoceptors
- **Ritanserin**
  - Mechanism
    - blocks 5-HT_2 receptors
- **Ondansetron**
  - Mechanism
    - 5-HT_3 antagonist
  - Clinical Applications
    - 預防癌症治療〈化學藥物治療或放射線治療〉所引起的噁心嘔吐，或手術後引. 起的噁心嘔吐

The Ergot Alkaloids

Effects of some ergot alkaloids at several receptors

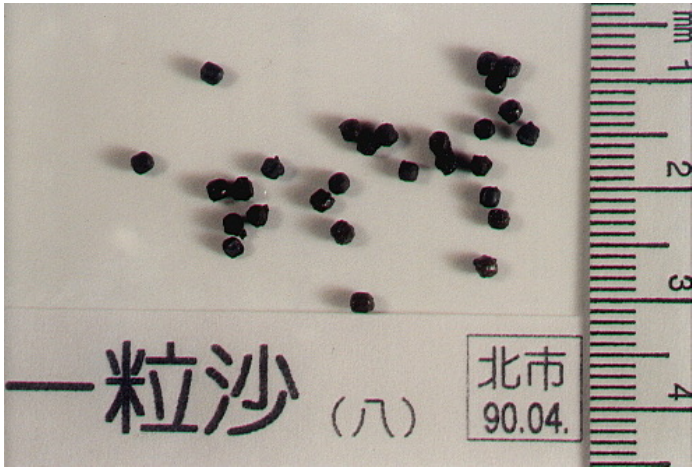
Ergot Alkaloid	Alpha Receptor (α_1)	Dopamine Receptor (D_2)	Serotonin Receptor (5-HT_2)	Uterine Smooth Muscle Stimulation
Bromocriptine	–	+++	–	0
Ergonovine	+	+	– (PA)	+++
Ergotamine	– (PA)	0	+ (PA)	+++
Lysergic acid diethylamide (LSD)	+/0	+++	– –/++ in CNS	+

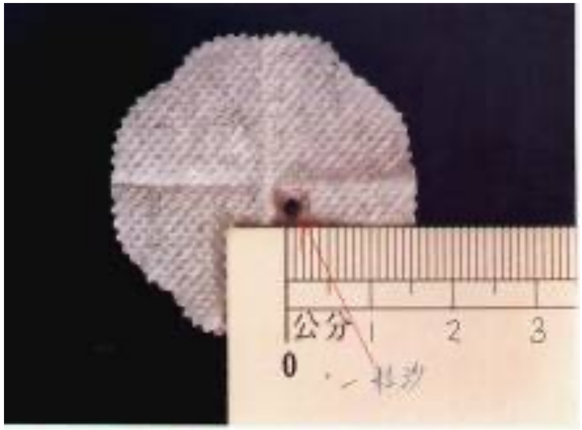
Organ System Effects The Ergot Alkaloids

- Central Nervous System
  - Lysergic acid diethylamide (LSD; "acid") is a synthetic ergot compound that clearly demonstrates this action.
  - The drug has been used in the laboratory as a potent peripheral 5-HT$_2$ antagonist, but good evidence suggests that its behavioral effects are mediated by ***agonist*** effects at prejunctional or postjunctional 5-HT$_2$ receptors in the central nervous system.
- Of all the currently available ergot derivatives
  - bromocriptine, **cabergoline (Dostinex®), and pergolide** have the highest selectivity for the pituitary dopamine receptors.
    - These drugs directly suppress prolactin secretion from pituitary cells by activating regulatory dopamine receptors
      - They compete for binding to these sites with dopamine itself and with other dopamine agonists such as apomorphine.

Lysergic acid diethylamide(LSD)

- History
  - 1938年亞伯特 霍夫曼(Albert Hofmann)在研究麥角生物鹼時，無意中合成了現在為大家所熟知的迷幻劑LSD；為一種麥角生物鹼衍生物
    - 0.01mg 便會產生作用
  - 別名
    - 搖腳丸、一粒砂、蟑螂屎、陽光、加州陽光…等
- 症狀
  - 心跳快、高血壓及發抖，會有情緒的起伏、時間的扭曲、視力錯覺(常看到物體或人身上鮮明的色彩會移動)、聲音會放大及扭曲、反射作用變強、無法走路、過度活動…
  - 使用LSD的病人，在戒斷不用LSD一段時間後，可能仍會有倒敘式精神異常，就如電影倒敘般，一一重新經歷以前的幻覺
- 屬於毒品危害防制條例第二級毒品





Clinical Pharmacology of Ergot Alkaloids

- Migraine
  - Ergot derivatives are highly specific for migraine pain; they are not analgesic for any other condition
    - **Ergotamine**
    - **Dihydroergotamine** (seglor®)
    - **Methysergide**
  - Noted
    - 當ergot衍生物與macrolides（例如：erythromycin）合併使用時，應小心監測是否有ergot中毒的表現（例如：周邊血管痙攣,四肢嚴重壞死）。
    - 不建議空腹使用
    - 嚴重肝機能不全和嚴重腎功能不全而未作血液透析患者，應謹慎使用。
    - 曾有動脈疾病病史者建議進行醫療監測（特別是冠狀動脈疾病和重度高血壓患者）。

cafergot®
(Ergotamine 1 mg + Caffeine 100 mg)
0
10
20
30 mm

seglor® 5mg
塞戈羅膠囊
DIHYDROERGOTAMINE MESYLATE
30
capsules
oral route
seglor® 5mg 30 capsules
Manufacturer:
Sanofi Winthrop Industrie - 33440 Ambarès - France
Keep out of the reach of children
GlaxoSmithKline
seglor® 5mg
Only on medical prescription
Administration:
Before use, read the leaflet inside carefully.
Swallow with glass of water.
STRICTLY FOLLOW THE PRESCRIBED DOSES

	Sumatriptan (Imigran®)	Ergotamine/caffeine (Cafergot®)	Dihydroergotamine (Seglor®)
劑型	50 mg/tab	1/100 mg/tab	5 mg/cap
建議劑量	25-100 mg立即服用，二小時後可再服用第二劑，每次極量100 mg，每日極量300 mg	1-2顆立即服用，每30分鐘可再服用一次，每日極量六顆，每週極量十顆	1顆 bid
適應症	有先兆或無先兆偏頭痛發作之急性緩解。 本藥僅適用於有明確診斷之偏頭痛	血管性頭痛、偏頭痛	偏頭痛

- Hyperprolactinemia
  - **Bromocriptine** →D_2 agonist→prolactin ⬇
    - The usual dosage of bromocriptine is 2.5 mg two or three times daily.
    - **Cabergoline** is similar but more potent.

- Postpartum Hemorrhage (產後出血)
  - ergot derivatives should be used only for control of late uterine bleeding and should never be given before delivery.
  - **Oxytocin** is the preferred agent for control of postpartum hemorrhage, but if this peptide agent is ineffective, ergonovine maleate, 0.2 mg given intramuscularly, can be tried.

Toxicity & Contraindications

- The most common toxic effects of the ergot derivatives are
  - gastrointestinal disturbances, including diarrhea, nausea, and vomiting.
- A more dangerous toxic effect of overdosage with agents like ergotamine and ergonovine is prolonged vasospasm.
- Chronic therapy with methysergide was associated with
  - connective tissue proliferation in the retroperitoneal space, the pleural cavity, and the endocardial tissue of the heart.
    - Retroperitoneal fibrosis, cardiac fibrosis, pleuropulmonary fibrosis
- Drowsiness

Thank You !